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Cancer Risk in Patients With Monoclonal Gammopathy of Undetermined Significance

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To assess the cancer risk of monoclonal gammopathy of undetermined significance (MGUS) we identified 1229 cases of MGUS in the period 1978 to 1993. Data on cancer occurrence in the MGUS cohort were obtained from the Danish Cancer Registry. The expected numbers of cancer cases were calculated from age-, sex-, county-, and period-specific cancer incidence rates. In the MGUS cohort 64 new cancers with a known association with M-components were diagnosed versus 5.0 expected giving a standardized incidence ratio (SIR) of 12.9 (95% confidence interval, 9.9–16.5). The relative risks of developing multiple myeloma (SIR 34.3), Waldenström's macroglobulinemia (SIR 63.8), and non-Hodgkin's lymphoma (SIR 5.9) were significantly increased and independent of time passed from detection of the M-component. The relative risk of chronic lymphocytic leukemia was not significantly increased, SIR 2.7 (0.5-7.7). Among cancer sites without known association with M-components 141 cases were observed versus 94.6 expected giving a SIR of 1.5 (1.3-1.8). This enhanced risk was seen for several non-hematological cancer sites but for most cancer sites the risk was dependent on time passed from detection of the M-component, indicating a bias rather than a causal role of MGUS. Am. J. Hematol. 63:1–6, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS) is characterized by the presence of a homogeneous monoclonal protein (M-component) in the serum of persons without evidence of multiple myeloma, Waldenström's macroglobulinemia, primary amyloidosis, or other lymphoproliferative disorders [1].

The prevalence of MGUS is age-related. Population-based studies from Sweden and France have reported a prevalence of MGUS of 3% in persons above 70 years of age and of 4% in those above 80 years [2,3]. Uncontrolled studies of MGUS patients clearly indicate an increased risk of developing symptomatic malignant monoclonal gammopathy, most often multiple myeloma and less frequently another malignant lymphoproliferative disorder [4,5].

It has been suggested that MGUS might present a preneoplastic state to certain nonhematological malignancies, and may be regarded as a marker of malignancy [6,7]. Data on the occurrence of nonhematological malignancies in MGUS patients are inconsistent. Clinical series have found an association between nonhematological malignancies and MGUS at the time of detection of the M-component [6–9]. Besides, two follow-up studies have observed a high incidence of nonhematological malignancies during the course of MGUS

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[5,7]. However, two cross-sectional studies of cancer patients found no association with monoclonal gammopathy [10,11], which contradicts the notion of M-components in serum as a paraneoplastic condition.

In the present study from Denmark, the incidence of multiple myeloma, other lymphoproliferative disorders, and nonhematological malignancies was assessed in a large cohort of patients with MGUS and compared with the appropriate rates of cancer in the general population.

SUBJECTS AND METHODS

The study was conducted in North Jutland County, Denmark, with 490,800 inhabitants (approximately 9% of the total Danish population). The county provides tax-supported health care for all inhabitants, i.e., guaranteed free access to family doctors and hospitals. Every citizen in Denmark is assigned a unique personal identification number (ID number) at birth, which enables linkage between different registries.

Study Population

Until 1994 the Departments of Clinical Chemistry at Hjørring and Aalborg Hospitals performed all serum and urine protein electrophoreses requested by hospital doctors and family doctors in North Jutland. The Microzone Electrophoresis System (Beckman® Instruments Inc., Fullerton, California) was used at Hjørring Hospital until 1988, and thereafter the electrophoresis was performed on agarose gel [12]. Agarose gel electrophoresis was used throughout the period at Aalborg Hospital. All sera with a suspected M-component were further examined at Aalborg Hospital by immunofixation using monospecific antibodies from Dakopatts A/S, Copenhagen, Denmark. The immunoglobulins were quantified by nephelometry.

The Department of Clinical Chemistry, Aalborg Hospital, has maintained a registry of all patients in North Jutland County with an identified M-component during the 16-year period from 1978 to 1993. The records contain information about patient's name and ID number, date of detection, type of M-component in serum, and concentration of immunoglobulins. During the study period 2563 patients with M-components were registered. All the members of this cohort were linked by their ID numbers to the Central Population Register to verify the ID number and to obtain dates of death or emigration. In addition, the 2,563 persons with a detected M-component were linked by their ID numbers to the the Danish Cancer Registry.

Hospital departments, family doctors, and practising specialists in Denmark are required to report all incident cases of cancer to the Danish Cancer Registry. Annual links to the Danish Hospital Discharge Registry and the National Death Certificate Files ensure that diagnoses of cancer that have not been reported to the Cancer Registry are subsequently included in the cancer files [13]. Comprehensive validation has shown that the completeness and validity of the Registry are 95–98% [14]. Diagnoses are coded according to a Danish version of the International Classification of Diseases, seventh revision (ICD-7).

We obtained information on the cancer diagnosis, if any, and the date of diagnosis. The persons with an M-component were classified as having MGUS if multiple myeloma (ICD-7 203.0–203.2), Waldenström's macroglobulinemia (203.3), non-Hodgkin's lymphoma (200, 202), or chronic lymphocytic leukemia (204.0) were not registered before or within 100 days from detection of the M-component. A period of 100 days was chosen from a practical point of view, because this interval is sufficient for follow-up investigations such as tissue biopsy and radiological examinations. In the period from 1978 to 1993, 1,324 cases of MGUS were identified. However, this procedure did not permit exclusion of patients with primary amyloidosis or heavy chain disease, two rare conditions not included in MGUS. Also, 95 patients with levels of IgG more than 30 g/l or levels of IgA or IgM more than 25 g/l were excluded in order to reduce the risk of including cases of asymptomatic myeloma. Thus, the study cohort consisted of 1,229 MGUS patients.

Cancer Incidence and Analysis

Follow-up for the occurrence of cancer began 100 days after detection of the M-component, and ended at the date of death, emigration, or December 31, 1993, whichever came first.

Multiplication of person-years under observation by the age-, sex-, county-, and period-specific incidence rates yielded the number of cancer cases expected in the MGUS cohort if the cohort members experienced the same risk as was prevalent in the county [15]. National incidence rates for Waldenström's macroglobulinemia were applied due to the low incidence of this malignancy. 95% confidence intervals for the standardized incidence ratios (SIR), i.e., the ratios of observed-to-expected number of cancer, were computed based on the assumption that the observed number of cancers in a specific category follows a Poisson distribution [16]. The cumulative risk of malignant transformation to multiple myeloma, Waldenström's macroglobulinemia, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia was calculated using the Kaplan & Meier method. In this study we have reserved the terms malignant transformation and M-component associated malignancies for the development of one of the above mentioned lymphoproliferative diseases in MGUS patients.

Ethics

The study was approved by the Regional Ethics Committee (no. 2-16-41-2-90 (93/12)), and special approval

TABLE I. Standardized Incidence Ratios (SIR) for M-Component Associated Cancer Sites in 1229 Patients With Monoclonal Gammopathy of Undetermined Significance

Cancer site (ICD-7 code)	Observed number	Expected number	SIR	95% confidence interval
All M-component associated sites	64	5.0	12.9	9.9–16.5
Multiple myeloma (203.0–203.2)				
Total	43	1.3	34.3	24.8–46.2
Male	13	0.7	17.8	9.4–30.3
Female	30	0.5	57.4	38.7–82.0
Follow-up (years)				
<1	11	0.2	47.4	23.6–84.9
1–4	22	0.6	34.2	21.4–51.7
5–9	5	0.3	15.6	5.0–36.3
10–16	5	0.1	86.2	27.8–201.1
Waldenström's macroglobulinemia (203.3)				
Total	3	0.05	63.8	12.8–186.3
Male	2	0.03	66.1	7.4–239
Female	1	0.02	59.5	0.8–331
Follow-up (years)				
<1	0	0.01	–	0.0–465
1–4	0	0.02	–	0.0–151
5–9	2	0.01	160.3	18.0–579
10–16	1	>0.01	438.6	5.7–2440
Non-Hodgkin's lymphoma (200, 202)				
Total	15	2.4	6.4	3.6–10.5
Male	5	1.2	4.1	1.3–9.6
Female	10	1.1	8.8	4.2–16.1
Follow-up (years)				
<1	6	0.4	14.3	5.2–31.0
1–4	6	1.2	5.0	1.8–10.8
5–9	3	0.6	4.9	1.0–14.3
10–16	0	0.1	–	0.0–31.5
Chronic lymphocytic leukemia (204.0)				
Total	3	1.1	2.7	0.5–7.7
Male	2	0.7	2.9	0.3–10.4
Female	1	0.4	2.3	0.0–12.7
Follow-up (years)				
<1	1	0.2	4.7	0.1–26.1
1–4	1	0.6	1.7	0.0–9.4
5–9	1	0.3	3.6	0.0–19.9
10–16	0	0.05	–	0.0–76,4

was obtained from the Danish Data Protection Agency (no. 1993-1110-1105).

RESULTS

The MGUS cohort comprised 622 males and 607 females, all together with a mean follow-up interval of 4.8 years (range, 0–15.7 years), totaling 5,898 person-years at risk. The mean age at MGUS was 67.9 years (range, 10–97 years). The serum M-component was IgA in 122 cases (9.9%), IgG in 813 (66.2%), IgM in 227 (18.5%), biclonal in 38 (3.1%), and exclusively light chain in 29 (2.4%). In IgA MGUS the median level of IgA was 9.3 g/l (range, 2.0–23.3 g/l), in IgG MGUS the median level of IgG was 15.0 g/l (2.0–29.9 g/l) and in IgM MGUS the median level of IgM was 6.2 g/l (1.0–24.6 g/l). Reference intervals for IgA were 0.8–3.3 g/l, for IgG 8.0–18.0 g/l, and for IgM 0.7–3.0 (females 0.3–2.2) g/l. Hypogammaglobulinemia was present in 281 (22.9%) of the 1,229 patients. Bence Jones proteinuria was detected in 58 (4.7%) of the patients.During follow-up, 64 cases of M-component associated malignancy were observed versus 5.0 expected, yielding a SIR of 12.9 (95% confidence interval, 9.9–16.5). The highly increased risk was mainly due to an excess of multiple myeloma, whereas excesses of Waldenström's macroglobulinemia and non-Hodgkin's lymphoma contributed to the overall excess to a minor degree. The risk for these malignancies was widely independent of time passed from detection of the M-component (Table I). The levels of IgA and IgG did not differ between the patients who developed multiple myeloma before or after 4 years from the MGUS diag-

TABLE II. Standardized Incidence Ratios (SIR) for Cancer Sites Without Known Association With M-Components in 1,229 Patients With Monoclonal Gammopathy of Undetermined Significance

	Follow-up, 0–16 years				Follow-up, 5–16 years			
Cancer site (ICD-7 code)	Observed number	Expected number	SIR	95% Confidence interval	Observed number	Expected number	SIR	95% Confidence interval
All non M-component associated sites	141	94.6	1.5	1.3–1.8	33	28.6	1.2	0.8–1.6
buccal cavity and pharynx (140–148)	5	2.0	2.5	0.8–5.8	3	0.6	5.0	1.0–14.6
Digestive organs (150–159)	39	25.9	1.5	1.1–2.1	7	7.6	0.9	0.4–1.9
Stomach (151)	10	4.0	2.5	1.2–4.6	3	1.1	2.7	0.6–8.0
Pancreas (157)	6	3.0	2.0	0.7–4.3	0	0.9	–	0–4.3
Respiratory system (160–164)	20	12.7	1.6	1.0–2.4	4	3.7	1.1	0.3–2.8
Lung (162)	18	11.3	1.6	0.9–2.5	4	3.3	1.2	0.3–3.1
Breast (170)	8	7.6	1.1	0.5–2.1	2	2.3	0.9	0.1–3.1
Female genital organs (171–176)	4	5.0	0.8	0.2–2.0	1	1.5	0.7	0.0–3.8
Male genital organs (177–179)	14	9.1	1.5	0.8–2.6	2	2.8	0.7	0.1–2.6
Prostate (177)	14	8.9	1.6	0.9–2.6	2	2.7	0.7	0.1–2.6
Urinary system (180–181)	14	8.9	1.6	0.9–2.7	5	2.7	1.9	0.6–4.3
Skin (190–191)	21	16.6	1.3	0.8–1.9	6	5.3	1.1	0.4–2.5
Brain and nervous system (193)	3	1.6	1.9	0.4–5.5	2	0.5	4.3	0.5–15.4
Bone and connective tissue (196, 197)	1	0.3	3.8	0.1–21.0	1	0.1	13.6	0.3–76
Acute nonlymphocytic leukemia	4	0.8	4.8	1.3–12.4	0	0.2	–	0.0–16.3
Miscellaneous hematological neoplasms[a]	1	0.5	2.0	0.1–10.9	0	0.1	–	0.0–23.4

[a]Hodgkin's disease (201), acute lymphocytic leukemia (214.0), and chronic nonlymphocytic leukemia (204.1).

nosis. The relative risk of chronic lymphocytic leukemia was not significantly increased, SIR 2.7 (0.5–7.7). To reduce any misclassification between CLL and non-Hodgkin's lymphoma all hospital records at diagnosis of the diseases were reviewed. The number of lymphocytes in CLL were in all cases considerable higher than 5×10^9/l, and in all cases of non-Hodgkin's lymphoma below this limit. The cumulative risk of malignant transformation was 8.8% (95% confidence interval, 6.2–11.4) at 10 years after assessment of MGUS.

The overall median survival of the MGUS patients calculated using the Kaplan & Meier method was 6.8 years. The median survival of MGUS patients who did not develop a malignant monoclonal gammopathy was 7.0 years. The median time to evolution of myeloma or Waldenstrom's disease when it developed was 2.4 and 7.8 years, respectively.

The distribution of M-component type among the 43 patients who developed multiple myeloma was 13 IgA, 29 IgG, and 1 light chain. All three patients who developed Waldenström's macroglobulinemia had M-components of the IgM type. The 15 patients with non-Hodgkin's lymphoma had the following distribution of M-components: 1 IgA, 5 IgG, 9 IgM. Two of the patients with CLL had IgM M-components whereas one patient had an IgG M-component.

141 cancers without known association with M-components were diagnosed versus 94.6 expected, giving a SIR of 1.5 (1.3–1.8) (Table II). The increased risk was seen for several non M-component associated cancer sites, but the risk was strongly influenced by time passed from detection of the M-component. Risk for all of these cancer sites diminished from 1.6 (1.3–2.0) during less than 5 years of follow-up to 1.2 (0.8–1.6) during more than 5 years after MGUS. With the exception of buccal cavity the risk was not significantly elevated for any of these cancer sites during late follow-up. For almost every one-year period included in early follow-up, the overall risk was significantly elevated (Fig. 1). Many different cancer sites contributed to the overall excesses, e.g., prostatic cancer (5 observed, SIR 3.1, 95% CI 1.0–7.1) within the first year, nonmelanoma skin cancer (7 observed, SIR 3.0, 95% CI 1.2–6.2) within the second year, and rectum cancer (4 observed, SIR 8.3, 95% CI 2.2–21.2) within the fifth year.

DISCUSSION

We found that the relative risk of multiple myeloma, Waldenström's macroglobulinemia, and non-Hodgkin's lymphoma was highly increased subsequent to the detection of MGUS, and with a cumulative risk at 10 years of 8.8%. It deserves notice that this risk was independent of time passed from detection of the M-component. Several studies have addressed the risk of multiple myeloma and malignant lymphoproliferative disorders in MGUS patients, and have demonstrated a cumulative risk of malignant transformation at 10 years of 15–19% [4,5,7,17,18]. However, in a Swedish population survey 6,995 persons over 25 years of age were screened with paper electrophoresis of which 64 persons had an M-component in the serum [2]. Two out of the 64 persons

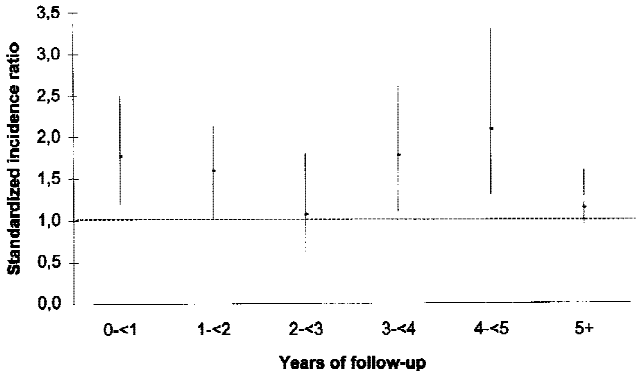

Fig. 1. Overall standardized incidence ratios (SIR) for cancer sites without known association with M-components according to time from detection of the serum M-component in a cohort of 1,229 patients with monoclonal gammopathy of undetermined significance.

had a B-cell malignancy at the time of the initial survey. A 20-year follow-up showed only one certain case of B-cell malignancy [19]. It is the only study on an unselected cohort of persons with MGUS, and it suggests a very low risk of malignant transformation.

All previous studies on malignant transformation have lacked reference populations. In our study the risk of malignancy was expressed as standardized incidence ratios, thus providing a comparison with the general population adjusting for gender and age of the persons in the MGUS cohort. In this context SIR is a more appropriate measure of cancer risk than the cumulative risk, which traditionally has been applied in all previous studies.

In some studies on MGUS, cases of chronic lymphocytic leukemia have arisen in the follow-up period [5,7], but it has never been determined whether MGUS implies a risk of chronic lymphocytic leukemia. In our study three cases of chronic lymphocytic leukemia occurred, but the SIR was not significantly increased.

Since MGUS is prevalent in the elderly population, only a fraction of persons with MGUS in North Jutland County were included in our study. There are various reasons for requesting a serum protein electrophoresis; it is often part of an evaluation of patients suffering from symptoms indicative of malignant disease. Consequently, cases of MGUS might be diagnosed by coincidence, and be associated accidentally with malignant disease. This potential bias in selection of study subjects implies that the increased risk of some types of cancer could be an artefact.

We made the assumption that MGUS is a chronic condition. Although transient M-components have been described following infections, long-term studies have shown disappearance of the serum M-component in only about 1% af patients after a median follow-up period of 11–22 years [5,7]. Because of the limitations of the exclusion procedure our study cohort might contain a few patients with either primary amyloidosis or heavy chain disease. However, these infrequent conditions are not likely to contribute essentially to the risk of cancer or to the total follow-up time. It is possible that the MGUS cohort does contain some cases of asymptomatic multiple myeloma due to the criterias for MGUS used in this study. This bias probably account for part of the highly increased risk of multiple myeloma within the first year after detection of the M-component and might overestimate the association between MGUS and multiple myeloma.

Agarose gel electroforesis is a more sensitive technique than paper electroforesis and will identify more of the small M-components. Paper electroforesis was used in Hjørring Hospital the first years of the study period. It is possible that a few patients with minor M-components and a possible low risk of malignant transformation have not been identified and not included in the MGUS cohort.

Several studies have shown occurrence of non-hematological malignancies in 3–16% of patients with monoclonal gammopathy, suggesting that M-components could be a paraneoplastic phenomenon [6–9]. An association with MGUS has been reported for cancer of the colon, prostate, breast, female genital organs, stomach, and lung. These studies have not applied reference populations, and they account insufficiently for the sampling procedure. Two studies have applied reference populations. In an American study, M-components were detected in only 0.65% of 5,066 patients with known or suspected malignancy [10]. The Swedish population survey was used as a reference population, and a similarity of the age and sex distribution was taken as an indication of the fortuitous association between MGUS and cancer. Another study showed that the incidence of monoclonal gammopathy in nonhematological malignancy did not differ from that of hospitalized controls [11]. Several hypotheses have been suggested to explain a possible association between M-components and nonhematological malignant disease, e.g., patients with an M-component having an increased risk of developing carcinoma due to disturbed immune surveillance, the M-component being an antibody against some antigen associated with the carcinoma, the globulin being the product of cancer cells, or coincidence [6]. It has also been suggested that the detection of M-components in some cancer patients arises from the incapacity of some analytical methods to detect more than the dominant clone of an oligoclonal pattern [11].

The study was suitable for an estimation of cancer risk in patients recognized with MGUS. We found that risk of several nonhematological malignancies was increased in the MGUS cohort. The decrease in risk with time suggests the impact of a bias rather than a causative role of MGUS. This bias was most clearly demonstrated for prostatic cancer, where the risk was significantly in-

creased within the first year after detection of the M-component, and after the first year gradual decreased with time. The bias in this case is probably due to the prominence of bone pain in prostatic cancer and multiple myeloma. Many other different types of cancer contributed to the overall excess seen within five years from detection of the M-component, so the excess is most likely due to differences in symptomatology and clinical course of these cancers and does not indicate a true association between MGUS and certain nonhematological cancers.

In conclusion, we confirmed the well-known excess risk of multiple myeloma and malignant lymphoproliferative disorders in MGUS, and provided a comparison with the general population. The risk was independent of time passed from detection of the M-component, thus emphasizing the importance of long-term evaluation of MGUS patients. The reported association between MGUS and certain nonhematological cancers is most likely an artefact due to the widespread use of serum protein electrophoresis as a diagnostic tool in patients suspected of having malignant disease.

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